REMARKS

Claims 100 and 101 have been cancelled and claims 111-116 have been added. Claims 35, 38, 68, 79, 85, 88 and 96 have been amended. Accordingly, claims 35-45, 68-77, 79-83, 85-93, 96-99 and 111-116 are currently pending in the present application.

It should be noted that the Official Action states that claims 34-44, 68-77, 79, 85-93, 96, 98 and 99 are pending and that claims 45, 80-83 and 97 have been withdrawn. Applicants believe that statement of pending claims recited in the Official Action is in error, and thus, Applicants respectfully request that a correction be made to include claims 45, 80-83 and 97 as pending.

No new matter has been added to the application. Support for each amendment can be found in the specification and/or the claims as originally filed. In particular, amendments to Claims 35, 85 and 96 are supported by the description, for example, on page 72, lines 10-17 and page 73 lines, 20-32. Support for amendments to claims 68 and 79 can be found on page 27, line 25 to page 28, line 23 and elsewhere throughout the specification. Claims 38 and 88 were amended to correct typographical errors.

The specific changes to the claims are shown on a separate set of pages attached hereto and entitled VERSION WITH MARKINGS TO SHOW CHANGES MADE, which follows the signature page of this Amendment. On this set of pages, the insertions are underlined while the **[deletions are in brackets and bolded]**.

Telephonic Interview

Applicants wish to thank the Examiner for extending the courtesy of a telephonic interview on July 25, 2002. The substance of the interview is reflected in the following remarks.

Claim rejections based on 35 U.S.C. § 112, second paragraph

Claim 35-44, 68-77, 79, 85-93, 96, 98 and 99 have been rejected as being indefinite for failing to particularly point out and distinctively claim the subject matter which Applicants regards as their invention. A response to each separate indefiniteness rejection is set out below.

Claim 35 was originally drawn to "a method for identifying compounds which reduce the activity or level of a gene product required for cell proliferation." Rather than consistently reciting the term "compounds," throughout the steps of claim 35, certain steps used the term

"compound." It was asserted that such wording made the claim unclear and therefore, clearer claim wording was requested. The same issue was asserted to be present in claim 85.

Claims 35 and 85 have been amended to recite the term "compound" consistently throughout each claim. As discussed in the telephonic interview of July 25, 2002, such amendment does not narrow the scope of the claim because the recited methods for screening a "compound" may be employed with one compound or with many compounds. Thus, as recited in the claims, the term "compound" is merely used to indicate that at least one compound is screened but that, in some embodiments, more than one compound is screened. In light of this clarifying amendment, Applicants respectfully, request that this basis of rejection be withdrawn.

Claims 35-44, 68-77, 79, 85-93, 96, 98 and 99 were asserted to be indefinite because none of the claims required that the gene product be utilized in the cell in a growth rate limiting step. Clarification was requested.

As was agreed upon in the telephonic interview of July 25, 2002, the practice of the methods of claims 35-44, 68-77, 79, 85-93, 96, 98 and 99 does not require reducing the level of a gene product to a point where that reduction constitutes a growth rate limiting step. This point is fully supported by the specification. For example, page 73, lines 22-32, show that assays may be successfully performed with cells that are sensitized over a wide inhibitory range that is less than rate limiting growth inhibition. Additionally, Example 9 (page 77, line 18 to page 78, line 9) shows the successful use of the methods described in the instant application with cells having less than rate limiting growth inhibition. Specifically, the cells in Example 9 were sensitized by expressing an antisense nucleic acid to reduce the level of *rplW* thereby reducing the growth rate of the cells by either 20% or 50% compared to that of the unsensitized control cells. When the sensitized cells were contacted with tetracycline, the further reduction in growth rate for both the 20% and 50% inhibited groups was much greater than the reduction in growth rate for unsensitized cells contacted with tetracycline (see Figure 2A). A similar example is shown using *elaD* as the essential gene target (see Figure 2B). Such evidence shows that the methods presently claimed in the instant application need not be performed only at levels of cell sensitization that is growth rate limiting. Accordingly, Applicants request that this basis for rejection of the pending claims be withdrawn.

Claims 35-44, 68-77, 79, 85-93, 96, 98 and 99 were asserted to be indefinite "due to lack of correspondence of the preamble with the actual claim steps." In particular, the Examiner

asserted that the claims were to methods of identifying compounds but no identification step was recited in the claims. Clarification was requested.

As discussed in the telephonic interview of July 25, 2002, independent claims 35, 68, 79, 85, and 96 have been amended to recite methods of "screening a candidate compound." Subsequently, it was agreed that in view of this amendment, no further amendments were required to satisfy the requirements of §112, second paragraph. Accordingly, the Applicants respectfully request that this basis for rejection be withdrawn.

Finally, it was asserted that the antecedent basis for the term "said cell" in claim 96 was vague and indefinite. Clarification was requested.

As discussed in the telephonic interview of July 25, 2002, claim 96 is a method of screening a candidate compound for the ability to inhibit cellular proliferation. The cell is contacted with an agent that reduces cellular proliferation. In the next recited step, the cell is contacted with the candidate compound. The amendment to claim 96 to include the term "candidate" in connection with the term "compound" eliminates any potential unclarity. Accordingly, the Applicants respectfully request that this basis for objection be withdrawn.

Claim rejections based on 35 U.S.C. § 103(a)

Claims 35, 36, 44, 85, 86, 96 and 98 were rejected on under 35 U.S.C. § 103(a) as being obvious over Muller et al.. It is asserted that Muller et al. teaches the combination therapy of antisense oligonucleotides with chemotherapeutics. Additionally, it is asserted that Muller et al. compared proliferation with and without various agents.

As suggested in the telephonic interview of July 25, 2002, independent claims 35, 85 and 96 have been amended to recite methods of screening a candidate compound wherein the candidate compound is not previously known to reduce proliferation. As agreed during the interview, this amendment distinguishes claims 35, 85, and 96, as well as claims dependent thereon, from the teachings of Muller et al..

Muller et al. provide a therapeutic method in which an antisense nucleic acid is administered to a patient in conjunction with a known chemotherapeutic compound. In contrast, the recited methods are not therapeutic methods but are methods in which sensitized cells are used to screen compounds not previously known to possess the ability to reduce proliferation for such an ability. As discussed in the telephonic interview, the claimed methods facilitate the

identification of compounds which reduce proliferation because they enable the detection of lead compounds which might escape detection using standard methods because they do not have sufficient potency to reduce the proliferation of an unsensitized cell. Because Muller discloses a therapeutic method in which an antisense nucleic acid is administered to a patient in conjunction with a known chemotherapeutic agent, Muller et al. does not teach or suggest the methods of the claimed invention. For example, among other things, Muller does not teach or suggest a method of using sensitized cells to screen compounds not previously known to possess the ability to reduce proliferation for such an ability.

In light of the foregoing, the Applicants respectfully request that the rejection of claims 35, 36, 44, 85, 86, 96 and 98 as obvious over Muller et al. be withdrawn.

CONCLUSION

Applicants believe that all outstanding issues in the Official Action have been resolved and that the present claims are in condition for allowance. Nevertheless, if any undeveloped issues remain or if any issues require clarification, the Examiner is invited to contact the undersigned at the telephone number provided below in order to expedite the resolution of such issues.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: _____

By: _____

Daniel Hart
Registration No. 40,637
Attorney of Record
620 Newport Center Drive
Sixteenth Floor
Newport Beach, CA 92660
(619) 235-8550

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35. (Amended) A method **[for identifying compounds which]** of screening a candidate compound for the ability to reduce the activity or level of a gene product required for cell proliferation, wherein said candidate compound is not previously known to possess the ability to reduce cell proliferation, said method comprising the steps of:

expressing an antisense nucleic acid against a nucleic acid encoding said gene product in a cell to reduce the activity or amount of said gene product in said cell, thereby producing a sensitized cell;

contacting said sensitized cell with a candidate compound; and

determining whether said candidate compound inhibits the growth of said sensitized cell to a greater extent than said candidate compound inhibits the growth of a nonsensitized cell.

38. (Amended) The method of Claim 36, wherein said cell is from an organism selected from the group consisting of *Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum,* **[*campylobacter*]** *Campylobacter jejuni, and Chlamydia trachomatus, Chlamydia pneumoniae* or any species falling within the genera of any of the above species.

68. (Amended) A method **[for assaying a compound]** of screening a candidate compound for the ability to inhibit proliferation of a microorganism said method comprising:

(a) identifying a gene or gene product required for proliferation in a first microorganism;

(b) identifying a homolog of said gene or gene product in a second microorganism;

(c) identifying an inhibitory nucleic acid sequence which inhibits the activity of said homolog in said second **[microorganism]** microorganism;

(d) contacting said second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid, thus sensitizing said second microorganism;

(e) contacting the sensitized microorganism of step (d) with a candidate compound; and

(f) determining whether said candidate compound inhibits proliferation of said sensitized microorganism to a greater extent than said candidate compound inhibits proliferation of a nonsensitized microorganism.

79. (Amended) A method of **[assaying a compound]** screening a candidate compound for the ability to inhibit proliferation said method comprising:

(a) identifying an inhibitory nucleic acid sequence which inhibits the activity of a gene or gene product required for proliferation in a first **[microorganism]** microorganism;

(b) contacting a second microorganism with a proliferation-inhibiting amount of said inhibitory nucleic acid, thus sensitizing said second microorganism;

(c) contacting the proliferation-inhibited microorganism of step (b) with a candidate compound; and

(d) determining whether said candidate compound inhibits proliferation of said sensitized second microorganism to a greater extent than said candidate compound inhibits proliferation of a nonsensitized second microorganism.

85. (Amended) A method **[for assaying compounds]** of screening a candidate compound for activity against a biological pathway required for proliferation, wherein said candidate compound is not previously known to possess the ability to reduce proliferation, said method comprising:

sensitizing a cell by expressing an antisense nucleic acid against a nucleic acid encoding a gene product required for proliferation in a cell to reduce the activity or amount of said gene product;

contacting the sensitized cell with a candidate compound; and

determining whether said candidate compound inhibits the growth of said sensitized cell to a greater extent than said candidate compound inhibits the growth of an nonsensitized cell.

88. (Amended) The method of Claim 85, wherein said cell is from an organism selected from the group consisting of *Staphylococcus aureus, Pseudomonas aeruginosa, Enterobacter cloacae, Helicobacter pylori, Neisseria gonorrhoeae, Enterococcus faecalis, Streptococcus pneumoniae, Haemophilus influenzae, Salmonella typhimurium, Saccharomyces cerevisiae, Candida albicans, Cryptococcus neoformans, Aspergillus fumigatus, Klebsiella pneumoniae, Salmonella typhi, Salmonella paratyphi, Salmonella cholerasuis, Staphylococcus epidermidis, Mycobacterium tuberculosis, Mycobacterium leprae, Treponema pallidum, Bacillus anthracis, Yersinia pestis, Clostridium botulinum,* **[*campylobacter*]** *Campylobacter jejuni, and Chlamydia trachomatus, Chlamydia pneumoniae* or any species falling within the genera of any of the above species.

96. (Amended) A method **[for assaying a compound]** of screening a candidate compound for the ability to inhibit cellular proliferation, wherein said candidate compound is not previously known to possess the ability to inhibit cellular proliferation, said method comprising:

contacting a cell with an agent which reduces the activity or level of a gene product required for proliferation of said cell;

contacting said cell with a candidate compound; and

determining whether said candidate compound reduces proliferation to a greater extent than said candidate compound reduces proliferation of **[cells]** a cell which **[have]** has not been contacted with said agent.